UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,575	07/14/2008	Robyn Lynne Ward	037775-0107	4121

22428 7590 03/14/2011

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
03/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/576,575	**Applicant(s)** WARD ET AL.	
	Examiner AMANDA SHAW	**Art Unit** 1634	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 March 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Amanda Shaw/
Examiner 1634

Continuation of 11. does NOT place the application in condition for allowance because: In the response filed on March 7, 2011 the Applicants argued (page 4) that Waki does not suggest but rather teaches away from the claimed invention. Applicants argue that based on Table 1 of Waki one or skill in the art would have gleaned that for a variety of tumors there is no methylation in a diversity of organs. However the applicants state that their present teachings indicate that one should find methylation of hMLH1 in a diversity of organs from individuals who have had cancers in which hMLH1 was methylated. The Applicants state that, according to Waki to assess the early development of cancer or if one will develop cancer, one should assay for the presence of an epimutation in the tissue in which the disease is developing or will develop. As such Applicant argue that this would have led the skilled artisan away from an expectation that the risk of developing disease could be assessed by searching for methylation in organs that had not developed and would not develop cancer. These arguments have been fully considered but are not persuasive. The claims are drawn to an assay for assessing the risk of cancer, which encompass any type of cancer, including gastric cancer. Waki teaches that methylation of hMLH1 was present in both neoplastic and non neoplastic gastric epithelia as follows 32% (30 our of 94_ and 24% (23 our of 94) (page 400, col 2). Waki states that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract). Therefore Waki teaches that the risk of gastric cancer in a healthy individual can be assessed by detecting hMLH1 methylation in gastric epithelia. Here it is noted that the claims do not specifically require determining the risk of developing cancer by detecting methylation in organs that have not developed and will not develop cancer. The claims only require determining methylation in a single population of cells from normal tissue. There is no requirement that the population of cells be obtained from different organs. Further there is no requirement that the normal tissue is tissue that had not developed and would not develop cancer.

Additionally the Applicants state that Waki's Table 1 shows no epimutation for hMLH1, and yet the patients later developed cancer. Therefore Applicants state that the skilled artisan would not have intuited how or even whether to predict risk of cancer from the results shown in Table 1. This argument has been fully considered but is not persuasive. Waki is not claiming to be able to predict any type of cancer by detecting hMLH1 methylation in any tumor type. Waki only teaches that detection of hMLH1 methylation in non neoplastic gastric epithelia may be useful for screening patients who may be at risk of developing gastric cancer (abstract).

The Applicants also argue that Waki lacks the sort of negative control that might have prompted the skilled artisan to pursue an approach akin to applicants. That is Waki omits any case where epimutation was lacking and the patient did not develop cancer. Waki also shows no case where there was epimutation in a healthy individual who later developed cancer. This argument has been fully considered but is not persuasive. When a reference relied on expressly anticipates or makes obvious the elements of the claimed invention, the reference is presumed to be enabling. Just because Waki did not use the same controls as the applicants does not mean that the Waki is not enabled for detecting the risk of developing gastric cancer by detecting hMLH1 methylation in non neoplastic gastric epithelia.

The Applicants argue (pages 5-7) that Okamoto cannot be combined with Waki. The Applicants state that claimed invention explicitly excludes parent of origin specific genes. The Applicants argue that Okamoto teaches a gene that is not parent of origin specific. Therefore one of skill in the art would have appreciated that Waki and Okamoto can not be combined. The Applicants state that none of the KSR considerations could have justified this apples versus oranges conflation of teachings. These arguments have been fully considered but are not persuasive. As previously pointed out Okamoto is relied on only to establish that it was known in the prior art how to quantitatively determine the frequency of epimutation of a particular gene in a population of cells. The Applicants have not provided any evidence that the method of quantitatively determining the frequency of epimutation of H19 could not also be used to quantitatively determine the frequency of epimutation of hMLH1. Regardless of whether a gene is subject to normal parent or origin specific expression or not, the frequency of epimutation is quantitated the same way. Because Waki and Okamoto both deal with detecting epimutation the references are combinable. Further motivation is present and has been provided in the rejection.

Further the Applicants argue (pages 7-8) that the claimed invention is keyed to detecting epimutation in tissues where disease will never occur, not on searching for epimutation in the tissue where disease is expected to arise. They argue that this notion is not even hinted by the prior art of Waki and Okamoto. This argument has been fully considered but is not persuasive. It is noted that the claims do not require detecting epimutation in tissues where disease will never occur. The claims require detecting epimutation in a population of cells from normal tissue, which would encompass normal tissue adjacent to neoplastic tissue. The use of distant tissue is only recited in claims 2-3. However Okamoto teaches a method wherein the methylation status of a part of the H19 promoter was examined in the unaffected adjacent kidney and peripheral blood of a Wilms tumor patient to determine if aberrant methylation of H19 was present in normal tissues. As such Okamoto teaches a method wherein epimutation is detected in normal tissue (i.e. the peripheral blood). For these reasons the rejections are maintained.